Gastric Cancer (2003) 6: 153–158
DOI 10.1007/s10120-003-0244-5

Original article

Biweekly administration regimen of docetaxel combined with CPT-11 in patients with inoperable or recurrent gastric cancer

Takashi Yoshioka[1], Yuh Sakata[2], Masanori Terashima[3], Kouji Sekikawa[4], Makio Gamoh[5], Yasushi Mitachi[6], Soh Saitoh[7], and Ryunosuke Kanamaru[1]

[1] Department of Clinical Oncology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan
[2] Misawa City Hospital, Misawa, Japan
[3] Iwate Medical University, Morioka, Japan
[4] Fukushima Medical University, Fukushima, Japan
[5] Ogawara Municipal Hospital, Ogawara, Japan
[6] Sendai Kousei Hospital, Sendai, Japan
[7] Aomori Prefectural Central Hospital, Aomori, Japan

Abstract

Background. **Both docetaxel (TXT) and irinotecan (CPT-11) are active chemotherapeutic agents for gastric cancer. We designed a biweekly administration regimen of TXT combined with CPT-11 for 4 weeks as one cycle in patients with inoperable or recurrent gastric cancer, and conducted a dose-escalation study.**

Methods. **Patients with histologically confirmed gastric cancer were treated with the regimen. The dosage levels of TXT and CPT-11 were as follows: level 1, 30 mg/m^2 and 50 mg/m^2; level 2, 35 and 50 mg/m^2; level 3, 40 and 50 mg/m^2; level 4, 40 and 60 mg/m^2; and level 5, 50 and 60 mg/m^2. The dose escalation was based on the dose-limiting toxicity (DLT) observed during the first cycle.**

Results. **Grade 4 neutropenia was observed at level 3, but no other DLT was observed at less than level 4 during the first cycle. However, three patients at level 3 could not continue treatment without a decrease in the dosage after the second cycle. Based on these results, level 2 was considered to be the clinically recommended dosages.**

Conclusion. **Biweekly TXT and CPT-11 was well tolerated. The recommended dosages of TXT and CPT-11 for a phase II trial are 35 mg/m^2 and 50 mg/m^2, respectively.**

Key words Chemotherapy · Docetaxel (TXT) · Gastric cancer · Irinotecan (CPT-11)

Introduction

Gastric cancer continues to be one of the most common malignancies in Japan. The development of diagnostic modalities and surgical techniques has improved the prognosis, but the associated mortality is still second highest next to lung cancer [1]. This mortality is due to the lack of an effective treatment for inoperable or recurrent gastric cancer, and it is very important to develop an effective treatment, especially in regard to chemotherapy.

A number of agents are active in advanced, metastatic gastric cancer, and chemotherapy has been seen to provide a significant benefit in the duration and quality of life over best supportive care alone [2]. However, for most trials with different combinations, including the most active single agents, median survival times remain low, ranging from 6 to 11 months, and several phase III studies show no differences in response or survival among different combinations [3–10]. While no one combination treatment regimen is recognized as the standard for gastric cancer, continuous infusion of 5-fluorouracil (FU) with cisplatin is currently considered to be a suitable reference treatment worldwide.

Recently several agents have emerged as potential new options for advanced gastric cancer. Promising data have been generated with docetaxel (TXT; Taxotere; Aventis Pharma, Schiltigheim, France) [11,12], paclitaxel (TXL; Taxol; Bristol-Myers Squibb, New York, NY, USA) [13], irinotecan hydrochloride (CPT-11) [14], and tegafur · gimeracil · oteracil potassium (TS-1) [15].

TXT is a novel semisynthetic taxoid obtained from 10-deaceryl baccatin III, a precursor extracted from the needles of the European yew, *Taxus baccata*. It works as an antimitotic agent, enhancing microtubule assembly and inhibiting the depolymerization of tubulin, resulting in the inability of cells to divide [16]. A late phase II study of TXT in advanced or recurrent gastric cancer was conducted in Japan [11,12]. The overall response

Offprint requests to: T. Yoshioka
Received: December 17, 2002 / Accepted: May 15, 2003

rate for the 129 eligible patients was 17.1%. Of the 96 patients previously treated with chemotherapy, 16.7% responded, compared with 18.2% of the 33 chemotherapy-naïve patients. Primary lesions and metastatic lesions in the liver and abdominal cavity responded in 6%, 19.6%, and 41.2% of cases, respectively. The incidences of grade 3/4 toxicities were: neutropenia, 84.6%; leukopenia, 65.3%; alopecia, 16.7%; anorexia, 10.9%; general fatigue, 8.7%; anemia, 7.7%; nausea and/or vomiting, 6.9%; thrombocytopenia, 3.2%; and diarrhea, 2.9% [11,12].

CPT-11 (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin) is a semisynthetic, water-soluble derivative of camptothecin (CPT), a plant alkaloid obtained from *Camptotheca acuminate*. CPT shows potent antitumor activity but intolerable toxicity. CPT-11, which retains the original antitumor activity of CPT but with less toxicity, was subsequently synthesized in Japan. After conversion to its active metabolite, SN-38, CPT-11 acts by inhibiting the eukaryotic enzyme DNA-topoisomerase I [17,18]. A late phase II study of CPT-11 in advanced or recurrent gastric cancer patients compared two intravenous dosage schedules: 100 mg/m^2 once a week, and 150 mg/m^2 once every 2 weeks [14]. The overall response rate for the 76 eligible patients was 18%. Of the 56 patients previously treated with chemotherapy, 16% responded, compared with 25% of the 20 chemotherapy-naïve patients. Primary lesions and metastatic lesions in the lymph nodes, lungs, and liver responded in 4.5%, 36.4%, 33.3%, and 17.4% of cases, respectively. The incidences of grade 3/4 toxicities observed in the 76 eligible patients were: leukopenia, 42.1%; nausea and/or vomiting, 11.8%; alopecia, 15.8%; anorexia, 19.7%; diarrhea, 22.4%; anemia, 28.9%; and thrombocytopenia, 6.6% [14].

We designed a biweekly (once every 2 weeks) administration regimen of TXT and CPT-11 in patients with inoperable or recurrent gastric cancer. The rationale for this combination is that the drugs have different action mechanisms and safety profiles. The biweekly administration of TXT might make it possible to avoid neutropenia, which is the dose-limiting toxicity (DLT) of TXT, without the need to administer granulocyte colony-stimulating factor (GCS-F). For chemotherapy in patients with gastric cancer, 5-FU derivatives and 5-FU based regimens are generally used. Our combination of TXT and CPT-11 may potentially be used in patients who are resistant to those regimens.

We performed a dose-escalation study of biweekly administration of TXT combined with CPT-11 in patients with inoperable or recurrent gastric cancer. The objectives of this study were to assess the safety and toxicity profiles of this regimen and to determine the DLT and the maximum-tolerated dose (MTD), or recommended dose, for a phase II study.

Patients and methods

Patient selection

Patients with histologically confirmed inoperable or recurrent gastric cancer with measurable or evaluable lesions who had been administered less than one regimen as previous chemotherapy, except for adjuvant therapy, were eligible to participate in this study. Other eligibility criteria included an Eastern Clinical Oncology Group (ECOG) scale performance status of 2 or less; age between 20 and 75 years; life expectancy of at least 3 months; provision of written informed consent in accordance with government and institutional guidelines; and adequate organ function (defined by a WBC count of $\geqq$4000/mm^3 and $\leqq$12000/mm^3, an absolute neutrophil count of $\geqq$2000/mm^3, a platelet count of $\geqq 10 \times 10^4$/mm^3; hemoglobin, $\geqq$9.0 g/dl; total bilirubin, $\leqq$1.5 mg/dl; GOT and GPT levels $\leqq$1.5 times the upper limit of normal or 3 times the upper limit of normal if liver metastases were present; alkaline phosphatase $\leqq$2.5 times the upper limit of normal except in the presence of bone metastases; and serum creatinine and blood urea nitrogen levels $\leqq$ the upper limits of normal). Exclusion criteria included the following: chemotherapy within 4 weeks before study entry (2 weeks for oral antimetabolic and biological response modifiers (BRM) agents); prior chemotherapy with TXT, TXL, or CPT-11; past history of allergic reactions to agents including polysorbate 80; peritoneal dissemination with unresolved bowel obstruction/subobstruction or a large amount of ascites; concomitant uncontrolled, nonmalignant disease (malignant hypertension, cardiac, pulmonary, renal, or hepatic disease; active infection); motor paralysis or peripheral neuropathy; the retention of pleural effusion or pericardial effusion that should be treated; diarrhea more than four times per day; active double cancer; pregnancy; brain metastases with any symptoms; steroid usage; or a prior history of the treatment of psychiatric diseases. Patients with obvious interstitial pneumonitis or pulmonary fibrosis on chest X-rays or computed tomographic (CT) scans were also excluded. The protocols were approved by the ethics committee of each institution.

Treatment regimens

TXT was diluted in 250 ml of 5% glucose or saline and administered as a 90-min IV infusion. CPT-11 (Daiichi Pharmaceutical, Tokyo, Japan and Yakult Honsha, Tokyo, Japan), diluted in 250 ml of 5% glucose or saline, was administered as a 90-min IV infusion just after completion of TXT administration. Both were administered on days 1 and 15, and this treatment course was repeated every 4 weeks with allowance for a delay in

Table 1. Dosage levels

Dosage level	TXT (mg/m^2)	CPT-11 (mg/m^2)	No. of enrolled patients
1	30	50	3
2	35	50	3
3	40	50	6
4	40	60	None
5	50	60	None

TXT, docetaxel; CPT-11, irinotecan

treatment if toxicity was seen. The starting doses of TXT and CPT-11 were 30 mg/m^2 and 50 mg/m^2, respectively. These doses were based on our preliminary data (unpublished). The escalation procedure is shown in Table 1.

For the purposes of determining the MTD, only DLTs occurring during the first cycle of therapy were considered. DLTs were defined as any of the following: grade 4 neutropenia lasting at least 3 days or grade 3 or 4 neutropenia associated with fever of 38.0 °C or more; grade 4 thrombocytopenia; grade 2 or higher renal dysfunction; grade 3 or 4 liver dysfunction; grade 3 or 4 nonhematologic toxicity, except for nausea, vomiting, appetite loss, or alopecia; or delay of more than 14 days in initiating the second cycle of therapy because of not fulfilling the same organ function criteria as those at the initiation of treatment or because of persistent toxicity of grade 2 or higher, except for nausea, vomiting, and alopecia. If one or more patients at a dose level experienced DLT, then three additional patients were treated at that dose level. The MTD was defined as the dose level that resulted in at least three of six patients developing the same DLT. The recommended dose was to be the dose immediately below the MTD.

Pretreatment and follow-up studies

Before the initiation of therapy, all patients had their history taken, and physical examination, assessment of ECOG scale performance status, chest X-rays, and a 12-lead electrocardiogram were performed. The extent of disease was determined by gastrointestinal X-rays, endoscopic examination of the upper gastrointestinal tract, abdominal ultrasonography, and a CT scan. Urinalysis; examination of tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen (CA)-19–9, and α-fetoprotein; and routine laboratory studies that included a complete blood count with the differential WBC count, total protein, albumin, total bilirubin, GOT, GPT, alkaline phosphatase, lactate dehydrogenase, blood urea nitrogen, serum creatinine, electrolytes, and calcium levels were also performed. History, physical examination, a complete blood count, liver function tests, renal function tests, electrolytes, and urinalysis were assessed at least once per week during treatment. Before each course, appropriate investigations were repeated as necessary to evaluate the sites of marker lesions. The tumor responses of metastatic lesions were evaluated by CT scans according to the "response evaluation criteria in solid tumors (RECIST)" guidelines [19]. A complete response (CR) was defined as the disappearance of all target and nontarget lesions without any new lesions for at least 4 weeks. A partial response (PR) was defined as the disappearance of target lesions and the persistence of one or more nontarget lesions and/or the maintenance of a tumor marker level above the normal limits for at least 4 weeks, or at least a 30% decrease in the sum of the longest diameters of target lesions and no appearance of one or more new lesions, and/or unequivocal progression of existing nontarget lesions without new lesions for at least 4 weeks. Stable disease (SD) was defined as less than a 30% decrease and less than a 20% increase in the sum of the longest diameters of target lesions and no appearance of one or more new lesions, and/or no unequivocal progression of existing nontarget lesions for at least 4 weeks. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameters of target lesions, or the appearance of one or more new lesions, and/or unequivocal progression of existing nontarget lesions, or the appearance of any new lesions. Tumor responses of the primary site were evaluated by the X-ray and endoscopic evaluation criteria proposed by the Japanese Research Society for Gastric Cancer [20], but, in this study, the primary sites were managed as nontarget lesions according to RECIST. ECOG common toxicity criteria were applied for evaluation of the toxicity of this therapy [21].

Results

The characteristics of the 12 patients enrolled in this study are listed in Table 2. The median age was 67 years (range, 42 to 73 years) and five patients showed performance status 0, while six patients showed performance status 1. Six patients had received previous chemo-

therapy, and all those regimens had included 5-FU or its derivatives (Table 2).

All patients completed the first cycle of therapy and were assessable for toxicity. All of the toxicities observed during the first cycle of chemotherapy are listed in Tables 3 and 4. On level 3, one patient met the protocol-specified criteria for DLT, and that was grade 4 neutropenia lasting at least 3 days. This patient recovered from neutropenia with the administration of G-CSF, and the chemotherapy was able to be continued at the dosages of level 2 from the next cycle of therapy, for four courses. Three other patients enrolled at level 3 developed grade 3 neutropenia in the second cycle. In two of the three patients, the drug administrations were delayed for less than 7 days, beginning again on day 15 of the second cycle in one patient, and on day 1 of the third cycle in another patient.

Table 2. Patient characteristics

Characteristic	No. of patients
Patients enrolled	12
Male	10
Female	2
Age (years)	
Median	67
Range	42–73
PS	
0	5
1	6
2	1
Prior chemotherapy	
No	6
Yes	6
5′-DFUR	1
TS-1	3
CDDP + TS-1	1
FP	1

PS, performance status; 5′ DFUR, doxifluridine; TS-1, tegafur · gimeracil · oteracil potassium; CDDP, cisplatin; FP, combination therapy of 5-fluorouracil (FU) and cisplatin

In this study, dose-escalation of TXT and CPT-11 was conducted to level 3, and the MTD had not yet been decided due to the absence of DLTs during the first cycle of therapy. On level 3, however, therapy after the second cycle was not carried out according to the schedule in about half of the patients. We concluded that the recommended dosages of TXT and CPT-11 were those of level 2.

In this phase I study, the efficacy of the therapy was also evaluated, and the results are shown in Table 5. This combination therapy was effective in one-third of the patients on levels 2 and 3. The overall response rate was 25%. Moreover, the response rate in the patients with previous chemotherapy was 50%, and all of the previous chemotherapies included 5-FU or its derivatives (Table 2).

Discussion

Both TXT and CPT-11 are anticancer drugs with unique mechanisms of action, compared with other drugs used in the treatment of gastric cancer, such as 5-FU, doxorubicin, cisplatin, and mitomycin C. TXT is a mitotic spindle poison that promotes tubulin polymerization and inhibits depolymerization of microtubules [16]. CPT-11 is converted to SN-38, and SN-38 inhibits DNA topoisomerase I and the division of cancer cells [17,18]. TXT and CPT-11 have different mechanisms of action, and the combination of both drugs is expected to have additional or synergic effects. The toxicity common to both drugs is neutropenia, and it is severe in every 3-week schedule of TXT which is recommended, in terms of the dose intensity as the standard regimen [11,12,14]. Recently, Burstein et al. [22] reported that the administration of TXT on a weekly schedule was effective and well tolerated in women with metastatic breast cancer. Their data show that decreasing the amount of the drug and shortening the interval between administrations

Table 3. Hematologic adverse reactions

Toxicity	Dosage level	No. of patients	Grade (ECOG) of adverse reaction				Incidence of grade 4 (%)
			1	2	3	4	
Leukopenia	1	3	1	0	0	0	0
	2	3	0	1	1	0	0
	3	6	3	0	1	0	0
Neutropenia	1	3	0	1	0	0	0
	2	3	0	1	1	0	0
	3	6	1	1	1	1	16.6
Thrombocytopenia	1	3	0	0	0	0	0
	2	3	0	0	0	0	0
	3	6	0	0	0	0	0

ECOG, Eastern Clinical Oncology Group

Table 4. Nonhematologic adverse reactions

Toxicity	Dosage level	No. of patients	Grade (ECOG) of adverse reaction				Incidence of grade 4 (%)
			1	2	3	4	
Nausea	1	3	1	0	0	0	0
	2	3	1	1	0	0	0
	3	6	2	1	0	0	0
Vomiting	1	3	0	0	0	0	0
	2	3	1	0	0	0	0
	3	6	2	0	0	0	0
Diarrhea	1	3	0	0	0	0	0
	2	3	1	0	0	0	0
	3	6	0	1	0	0	0
Appetite loss	1	3	1	1	0	0	0
	2	3	0	0	1	0	33.3
	3	6	2	0	1	0	16.6
Neuropathy (sensory)	1	3	0	0	0	0	0
	2	3	1	0	0	0	0
	3	6	0	0	0	0	0

Table 5. Objective response

Dosage level	Previous chemotherapy	No. of patients	No. of patients with each clinical response				Response rate (%)
			CR	PR	SD	PD	
1		3	0	0	2	1	0
2		3	0	1	2	0	33.3
3		6	0	2	1	3	33.3
	No	6	0	0	3	3	0
	Yes	6	0	3	2	1	50
Overall		12	0	3	5	4	25

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

makes it possible to maintain the efficacy but avoid the neutropenia. For these reasons, we designed a biweekly administration of TXT and CPT-11 in patients with inoperable or recurrent gastric cancer.

In this dose-escalation study, the MTD could not be determined, due to the absence of DLTs. There was also no grade 3 or 4 nonhematologic toxicity, but some patients could not continue the treatment after the second cycle according to the administration schedule (level 3). Moreover, the efficacy of the treatment was observed on level 2. It might be possible to escalate the dosage of CPT-11, fixing TXT at 35 mg/m^2, but this should be studied in another trial in future. Therefore, we decided that 40 mg/m^2 of TXT and 50 mg/m^2 of CPT-11 was a nontolerable dose for continuing the treatment, and we recommend 35 mg/m^2 of TXT and 50 mg/m^2 of CPT-11 for the phase II study of this combination therapy.

Recent treatment regimens under development for advanced gastric cancer include the following combinations: cisplatin/5-FU (FP) [3], sequential high-dose methotrexate and 5-FU/doxorubicin (FAMTX) [4], etoposide/leucovorin/5-FU (ELF) [5], epi-doxorubicin/cisplatin/5-FU (ECF) [6], and variants of these regimens. Wils et al. [7] reported that FAMTX had significant clinical benefits in terms of response and survival compared with doxorubicin/mitomycin C/5-FU (FAM), which is a classical regimen. Kim et al. [8] reported that FP had a significant benefit in terms of response compared with FAM and 5-FU only, but there was no difference in survival. In the European Organization for Research and Treatment of Cancer (EORTC) phase III study comparing FAMTX, ELF, and FP, no significant differences in response or survival have been found to date between the three treatment regimens [9]. Webb et al. [10] reported that ECF showed significant clinical benefits in terms of response and survival compared with FAMTX. At present no one combination treatment regimen is recognized as the standard for gastric cancer, but all candidates include 5-FU or its deriva-

tives. Our combination treatment does not include 5-FU or its derivatives, and in spite of the very small study population, our combination treatment showed a high response rate in patients with previous chemotherapy that involved 5-FU or its derivatives. This result shows that the combination of TXT and CPT-11 has potential as a second-line treatment for patients who have failed to respond to regimens including 5-FU.

In conclusion, we conducted biweekly administration of TXT and CPT-11, and the recommended dosages were 35 mg/m^2 of TXT and 50 mg/m^2 of CPT-11. This combination seems to have potential as a second-line treatment in patients with inoperable or recurrent gastric cancer. A phase II study of this combination has been started.

Acknowledgments We thank Mr. Akira Nagai and Mr. Tsutomu Miyazawa for their secretarial assistance.

References

1. Cancer Statistics in Japan 2001. http://www.ncc.go.jp/en/statistics/2001/index.html
2. Wils J. The treatment of advanced gastric cancer. Semin Oncol 1996;23:397–406.
3. Lacave AJ, Baron FJ, Anton LM, Estrada E, De Sande LM, Palacio I, et al. Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer; a phase II trial. Ann Oncol 1991;2:751–4.
4. Klein HO, Wickramanayake PD, Dieterle F, Mohr R, Oerkermann H, Gross R. High-dose MTX / 5-FU and adriamycin for gastric cancer. Semin Oncol 1983;10:29–31.
5. Wilke H, Preusser P, Fink U, Achterrath W, Meyer HJ, Stahl M, et al. New developments in the treatment of gastric carcinoma. Semin Oncol 1990;17:61–70.
6. Findlay M, Cunningham D, Norman A, Mansi J, Nicolson M, Hickish T, et al. A phase II study in advanced gastroesophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994;5:609–16.
7. Wils J, Klein HO, Wagener DJT, Bleiberg H, Reis H, Korsten F, et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin — a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 1991;9:827–31.
8. Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC, et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer 1993;71:3813–8.
9. Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Custem E, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 2000;18:2648–57.
10. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15:261–7.
11. Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. Late phase II clinical study of RP56976 (Docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (Group A). Jpn J Cancer Chemother 1998;25:1915–24.
12. Mai M, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. A late phase II clinical study of RP56976 (Docetaxel) in patients with advanced or recurrent gastric cancer: a Japanese Cooperative Study Group trial (Group B). Jpn J Cancer Chemother 1999;26:1487–96.
13. Hyodo I, Ohtsu A, Shirao K, Miyata Y, Saito H, Taguchi T. Late phase II study of paclitaxel (BMS-181339) in patients with advanced/recurrent gastric cancer; a Japanese Cooperative Study Group trial (group A). The 38th Annual meeting of Japan Society for Cancer Therapy 2002;35:443.
14. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, et al. Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. Jpn J Cancer Chemother 1994;21:1033–8.
15. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur — 0.4 M gimestat — 1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998;34:1715–20.
16. Ringel I, Horwitz SB. Studies with RP56976 (Taxotere): a semisynthetic analogue of Taxol. J Natl Cancer Inst 1991;83:288–91.
17. Hsiang YH, Lihou MG, Liu LF. Arrest of replication forks by drug-stabilized topoisomerase I-DNA cleavable complexes as a mechanism of cell killing by camptothecin. Cancer Res 1989;49:5077–82.
18. Tanizawa A, Fujimori A, Fujimori Y, Pommier Y. Comparison of topoisomerase I inhibition, DNA damage and cytotoxicity of camptothecin derivatives presently in clinical trials. J Natl Cancer Inst 1994;86:836–42.
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
20. Japanese Research Society for Gastric Cancer. Japanese classification of gastric carcinoma. First English Ed. Tokyo: Kanehara; 1995.
21. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
22. Burstein HJ, Manola J, Younger J, Parker LM, Bunnell CA, Scheib R, et al. Docetaxel administered on a weekly basis for metastatic breast cancer. J Clin Oncol 2000;18:1212–9.